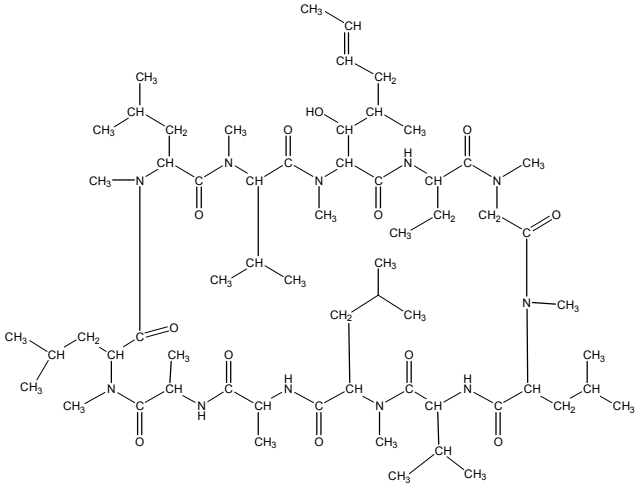
CYCLOSPORIN A (CICLOSPORIN)
CAS No. 59865-13-3
First listed in the *Eighth Report on Carcinogens*



CARCINOGENICITY

Cyclosporin A (CsA) is *known to be a human carcinogen* based on studies in humans which indicate a causal relationship between exposure to cyclosporin A and human cancer (IARC V.50, 1990).

There are numerous case reports (IARC V.50, 1990) describing cancer (mainly lymphoma or skin cancer) developing in organ transplant recipients, psoriasis patients, and rheumatoid arthritis patients treated with cyclosporin A for immunosuppression. Some of these patients were treated with cyclosporin alone, whereas others were treated with other immunosuppressive agents in combination with cyclosporin. The time between treatment initiation and tumor development ranged from as early as 1 month to 10 years. In some cases, tumors regress after discontinuation of treatment with cyclosporin. Several cohort studies also indicate that cyclosporin A is carcinogenic in humans, inducing a tumor incidence of less than 5% in the patient population (IARC V.50, 1990).

In grafted macaques, cyclosporin A increased the incidence of lymphomas, a neoplasm that occurs extremely infrequently in this species of monkeys. When given in combination with various other immunosuppressive regimens, cyclosporin A induced a substantial increase in the incidence of lymphomas when compared to immunosuppressive regimens excluding cyclosporin A. In mouse dietary studies, there was an increased incidence of thymic lymphoma in male mice administered 150 ppm cyclosporin A for 20 to 34 weeks, whereas the incidence of tumors of any organ was not increased in male mice administered 1, 4, or 16 ppm cyclosporin A for 78 weeks (IARC V.50, 1990). In rats, in a study in which there was no mention of control tumor incidence, renal tumors were detected in more than 50% of streptozotocin-induced diabetic animals administered 10 mg cyclosporin/kg bw orally for 20 weeks (Reddi et al., 1991). However, the incidence of tumors of any organ was not increased in rats administered 0.5, 2, or 8 mg cyclosporin A/kg bw orally for 95 (males) or 105 (females) weeks (IARC V.50, 1990).

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

In initiation-promotion studies, cyclosporin A increased the incidence of lymphoid tumors in male mice either irradiated or treated with *N*-methyl-*N*-nitrosourea (MNU) (IARC V.50, 1990), of hepatocellular carcinoma in male rats initiated with diethylnitrosamine (Masuhara et al., 1993), and of intestinal adenocarcinoma in male rats administered MNU (IARC V.50, 1990). Treatment with cyclosporin A also increased the incidence of cervical lymph node metastasis in Syrian golden hamsters treated with dimethylbenz[*a*]anthracene (Yamada et al., 1992), and metastasis of tumors to the liver in male mice inoculated via the portal vein with MCA 38 colon tumor cells (Yokoyama et al., 1994) or colon-26 tumor cells (Suzaki et al., 1995). In contrast, an increase in adenomas by cyclosporin A was not detected in male mice treated with urethane (IARC V.50, 1990), in male rats initiated with 3-methylcholanthrene (Bussiere et al., 1991), or in rats treated with *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (IARC V.50, 1990).

Cyclosporin A is reported as negative for the induction of genetic damage (gene mutations in prokaryotes, gene mutations and chromosomal aberrations in cultured mammalian cells, chromosomal aberrations and micronuclei in rodent bone marrow cells, DNA repair in mouse testicular cells, and dominant lethal mutations in male mice) (IARC V.50, 1990; Zwanenburg and Cordier, 1994). However, cyclosporin A was reported to induce a weak increase in sister chromatid exchanges in human lymphocytes *in vitro* and to induce unscheduled DNA synthesis and chromosomal aberrations in the peripheral blood lymphocytes of kidney transplant patients treated with cyclosporin A and prednisolone (IARC V.50, 1990).

The most likely explanation for the increased incidence of tumors in patients treated with cyclosporin A is immune suppression (Ryffel, 1992).

PROPERTIES

Cyclosporin A occurs as white prismatic crystals from acetone. It is insoluble in water and *n*-hexane and very soluble in all other organic solvents such as methanol, ethanol, acetone, ether, and chloroform. Cyclosporin A has a melting point of 148-151 °C (natural) and 149-150 °C (synthetic). It is stable in solution at temperatures below 30 °C but is sensitive to light, cold, and oxidization. When heated to decomposition, cyclosporin A emits toxic fumes of nitrogen oxides (NO_x).

USE

Cyclosporin A has been used as an immunosuppressive agent since the mid-1980s. It is used extensively in the prevention and treatment of graft-versus-host reactions in bone marrow transplantation and for the prevention of rejection of kidney, heart, and liver transplants. It has also been tested for the therapy of a large variety of other diseases in which immunological factors may have a pathogenetic role, including Graves' disease, uveitis, Crohn's disease, ulcerative colitis, chronic active hepatitis, primary biliary cirrhosis, diabetes mellitus, myasthenia gravis, sarcoidosis, dermatomyositis, systemic lupus erythematosus, psoriasis, rheumatoid arthritis, and certain nephropathies (IARC V.50, 1990; Reents, 1996). CsA is used alone or in combination with azathioprine, prednisolone, prednisone, antilymphocyte globulin, actinomycin, cyclophosphamide, methylprednisolone and/or phototherapy (e.g., PUVA, UVB). CsA is administered orally or intravenously (i.v.). Oral preparations may contain corn, castor, or olive

oil in ethanol; i.v. preparations contain 33% alcohol and a castor oil vehicle. In July 1995 a new microemulsion oral formula of CsA was approved by the FDA (Reents, 1996).

PRODUCTION

Cyclosporin A is manufactured commercially in Switzerland (IARC V.50, 1990). The 1998 Chemical Buyers Directory identified two American suppliers of the chemical (Tilton, 1997). Chem Sources also listed two suppliers (Chem Sources, 1996). No data on imports or exports of cyclosporin A were available.

EXPOSURE

The primary routes of potential human exposure to cyclosporin A are intravenous and oral administrations. Patients receiving organ transplants are exposed to cyclosporin. Potential occupational exposure may occur for workers formulating or packaging the solutions and for health care professionals administering the drug. A typical oral dose of cyclosporin A is 18 mg/kg daily, beginning 12 hours before transplantation and continuing for one to two weeks. The dosage may subsequently be reduced to 5 to 10 mg/kg or less. Cyclosporin A may also be given by intravenous administration at one-third the oral dose (IARC V.50, 1990). This drug is often given for several months to transplant recipients. Cyclosporin A is not included in the National Occupational Exposure Survey (1981-1983) or the National Occupational Hazard Survey (1970) conducted by NIOSH (1990).

REGULATIONS

FDA regulates cyclosporin under the Food, Drug, and Cosmetic Act (FD&CA) as a prescription peptide antibiotic drug. Purities and concentrations are given for cyclosporin oral and injectable dosage forms of drugs. FDA also regulates the use of cyclosporin in ophthalmic ointment for dogs. OSHA lists cyclosporin as a medication that a physician and the employer may wish to review. Regulations are summarized in Volume II, Table A-20.